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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/779,532	02/13/2004	Jeremy Green	VPI/99-109 DIV US	5593

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VERTEX PHARMACEUTICALS INC.
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EXAMINER

RAO, DEEPAK R

ART UNIT	PAPER NUMBER
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1624

DATE MAILED: 03/21/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/779,532

Applicant(s)

GREEN ET AL.

Examiner

Deepak Rao

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 14 February 2005.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-8 and 10-24 ~~is/are~~ are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,2,8 and 11-24 ~~is/are~~ are rejected.
- 7) ☒ Claim(s) 3-7 and 10 ~~is/are~~ are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date 02132004.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

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DETAILED ACTION

Claims 1-8 and 10-24 are pending in this application.

Election/Restrictions

Applicant's election without traverse of Group II, claims 1-8 and 10-24 in the reply filed on February 14, 2005 is acknowledged.

The election of the compound XIA-23 is also acknowledged, as the elected compound was not found in the prior art, the search was expanded to the genus of the elected invention of Group II.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 12-24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treatment of rheumatoid arthritis, does not reasonably provide enablement for the method of treatment or prevention of any disease state or condition that can be alleviated by a protein kinase inhibitor generally. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The instant claims are drawn to "a method treating a disease state or condition in mammals that is alleviated by treatment with a protein kinase inhibitor" and the specification

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provides a wide list of diverse disorders based on kinase inhibiting activity, see pages 45-48.

First, the instant claims cover 'disease states' or 'conditions' that are known to exist and those that may be discovered in the future, for which there is no enablement provided. The use disclosed in the specification is as protein kinase inhibitors, useful to treat a laundry list of diseases, which include cancer, inflammatory diseases, autoimmune diseases, neurodegenerative diseases, allergies, etc. Test assays and procedures are provided in the specification in Examples 38-42 related to JNK3, Src and Lck kinase inhibition, wherein the inhibitory activity data for some of the compounds (i.e., drawn to isoxazolyl-pyrimidinyl compounds) of the invention is provided in Table 8, however, there is nothing in the disclosure regarding how this *in vitro* data correlates to the treatment of the diverse disorders of the instant claims. Further, all the compounds actually tested are structurally very different from the other compounds of the claims (i.e., isoxazolyl vs. pyrazolyl vs. triazolyl vs. furyl) such that no reasonable extrapolation could be made by one skilled in the art regarding the activity of the instantly claimed compounds. The disorders encompassed by the instant claims include proliferative disorders, inflammatory diseases, neurodegenerative diseases, etc., some of which have been proven to be extremely difficult to treat. Further, there is no reasonable basis for assuming that the myriad of compounds embraced by the claims will all share the same physiological properties since they are so structurally dissimilar as to be chemically non-equivalent and there is no basis in the prior art for assuming the same. Note *In re Surrey*, 151 USPQ 724 regarding sufficiency of disclosure for a Markush group.

Further, the instant claims recite treating of diseases mediated by JNK, Src or Lck kinases, and there is no disclosure regarding how all these assorted types diseases are treated.

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See MPEP § 2164.03 for enablement requirements in cases directed to structure-specific arts such as the pharmaceutical art. Receptor activity is generally unpredictable and highly structure specific area, as evidenced by the wide range of results obtained for the tested compounds. It is inconceivable as to how the claimed compounds can treat the laundry list of diseases embraced by the claims having diverse mechanisms or inhibit the recited kinases.

A 'proliferative disorder' is anything that causes abnormal tissue growth. That can be growth by cellular proliferation more rapidly than normal, or continued growth after the stimulus that initiated the new growth has ceased, or lack (partial or complete) of structural organization and/or coordination with surrounding tissue. It can be benign or malignant. Thus, such term covers not only all cancers, but also covers precancerous conditions such as lumps, lesions, polyps, etc. No compound has ever been found to treat cancers of all types generally. Since this assertion is contrary to what is known in medicine, proof must be provided that this revolutionary assertion has merits. The existence of such a "silver bullet" is contrary to our present understanding of oncology. Cecil Textbook of Medicine states that "each specific type has unique biologic and clinical features that must be appreciated for proper diagnosis, treatment and study" (see the enclosed article, page 1004). Different types of cancers affect different organs and have different methods of growth and harm to the body. Also see *In re Buting*, 163 USPQ 689 (CCPA 1969), wherein 'evidence involving a single compound and two types of cancer, was held insufficient to establish the utility of the claims directed to disparate types of cancers'. Thus, it is beyond the skill of oncologists today to get an agent to be effective against cancers generally. In reference to cancer treatment using protein tyrosine kinase inhibitors, Traxler (Exp. Opin. Ther. Patents, 1997) stated that "pharmacological properties such as stability

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in biological media, bioavailability, metabolism or formulability are significant hurdles” see page 585, col. 2, lines 33-36.

The claims recite the use of the instantly claimed compounds in treating ‘angiogenic disorder’. Angiogenesis is the process of vascularization of a tissue involving the development of new capillary blood vessels and therefore, is not seen as being a disease or disorder, but as an absolutely essential body process. Thus, there is no enablement for treating something which is not itself a problem and is indeed essential for life.

Also, there is no common mechanism by which all inflammatory conditions arise. The mediators include bradykinin, serotonin, histamine, assorted leukotrienes, cytokines, etc. Accordingly, treatments for these diseases are normally tailored to the particular type of inflammation or infection present and there is no “magic bullet” against the plethora of diseases encompassed by the instant claims.

Further, the list of the diseases includes neurodegenerative diseases (see specification page 19) which covers diverse disorders such as Alzheimer’s disease, dementia, hereditary cerebellar ataxias, paraplegias, syringomyelia, phakomatoses, and much more. In fact, Layzer, Cecil Textbook of Medicine (article enclosed), states that “some degenerative diseases are difficult to classify because they involve multiple anatomic locations” (see page 2050). For example, Alzheimer’s disease has traditionally been very difficult or impossible to prevent or even to treat effectively with chemotherapeutic agents. See e.g., the Cecil Textbook of Medicine, 20th edition (1996), Vol. 2, wherein it is stated that “[t]here is no cure for Alzheimer’s disease, and no drug tried so far can alter the progress of the disease.” (pg. 1994).

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Further, the list of the diseases includes multiple sclerosis which has traditionally been very difficult or impossible to treat effectively with chemotherapeutic agents. See e.g., Casanova et al. (PubMed Abstract enclosed) state that "Multiple Sclerosis (MS) is a disorder in which the pathogenesis is not clearly understood", see the abstract.

The instant claims 15-22 recite 'wherein said method is used to treat or **prevent**' the diseases. Therefore, the scope of the claims includes not only treatment but also "**prevention** of a disease" which is not adequately enabled solely based on the kinase inhibitory activity of the compounds provided in the specification. "To prevent" actually means *to anticipate or counter in advance, to keep from happening etc.* (as per Webster's II Dictionary) and there is no disclosure as to how one skilled in the art can reasonably establish the basis and the type of subject to which the instant compounds can be administered in order to have the "prevention" effect. There is no evidence of record which would enable the skilled artisan in the identification of the people who have the potential of becoming afflicted with the disease(s) or disorder(s) claimed herein. Next, applicant's attention is drawn to the Revised Interim Utility and Written Description Guidelines, at 64 FR 71427 and 71440 (December 21, 1999) wherein it is emphasized that 'a claimed invention must have a specific and substantial utility'. The disclosure in the instant case is not sufficient to enable the instantly claimed 'preventive' effect solely based on the inhibitory activity disclosed for the compounds.

Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of

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unpredictability of the factors involved". See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Traxler, in a recent article (Exp. Opin. Ther. Patents, 1997) stated that "The concept of the inhibition of growth factor receptor-mediated signal transduction via inhibition of its protein tyrosine kinase is a novel, **not yet proven** clinical approach to the regulation of cell proliferation.", see page 585, col. 1. Therefore, the state of the art provides the need of undue experimentation for the instantly claimed therapeutic benefits.

(Only a few of the claimed diseases are discussed here to make the point of an insufficient disclosure, it does not definitely mean that the other diseases meet the enablement requirements).

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the use of the invention. In view of the breadth of the claim, the chemical nature of the invention, the unpredictability of ligand-receptor interactions in general, and the lack of working examples regarding the activity of the claimed compounds, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the invention commensurate in scope with the claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 15-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

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Claims 15-22 recite the limitation "treat or prevent" in line 2 of each of the claims. There is insufficient antecedent basis for this limitation in claim 12 on which these claims 15-22 are dependent. Claim 12 only recites "A method for treating".

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-2 and 11-24 are rejected under 35 U.S.C. 102(b) as being anticipated by Anantanarayan et al., WO 98/52940. The instant claims read on reference disclosed compounds, see the structural formula (I) in page 4 and the corresponding species in the Examples, particularly, Example A-213, A-220 to A-222, A-245 to A-248, etc. The reference compounds are also taught to be protein kinase inhibitors useful as pharmaceutical therapeutic agents, see page 10.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

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This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-2, 8 and 11-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Anantanarayan et al., WO 98/52940. The reference teaches a generic group of compounds which embraces applicant's instantly claimed compounds. See formula (I) in page 4 and the Examples A-213, A-220 to A-222, A-245 to A-248, etc. The compounds are taught to be useful as pharmaceutical therapeutic agents having kinase inhibitory activity, see pages 10+. Claims 1-2 and 11-24 read on the reference disclosed compounds and the use thereof as rejected under 35 U.S.C. 102(b) above. Claim 8 differs from the reference by reciting a specific species (as recited in section (f) of the claim) which fall within the reference disclosed genus. It would have been obvious to one having ordinary skill in the art at the time of the invention to select any of the species of the genus taught by the reference, including those instantly claimed, because the skilled chemist would have the reasonable expectation that any of the species of the genus would have similar properties and, thus, the same use as taught for the genus as a whole i.e., as pharmaceutical therapeutic agents. One of ordinary skill in the art would have been motivated to select the claimed compounds from the genus in the reference since such compounds would have been suggested by the reference as a whole. It has been held that a prior art disclosed genus of

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useful compounds is sufficient to render prima facie obvious a species falling within a genus. *In re Susi*, 440 F.2d 442, 169 USPQ 423, 425 (CCPA 1971), followed by the Federal Circuit in *Merck & Co. v. Biocraft Laboratories*, 847 F.2d 804, 10 USPQ 2d 1843, 1846 (Fed. Cir. 1989).

Allowable Subject Matter

Claims 3-7 and 10 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Receipt is acknowledged of the Information Disclosure Statement filed on February 13, 2004 and a copy is enclosed herewith.

Conclusion

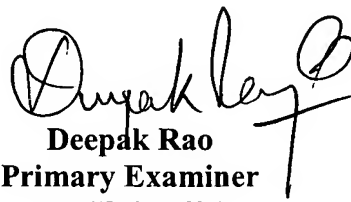
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deepak Rao whose telephone number is (571) 272-0672. The examiner can normally be reached on Tuesday-Friday from 6:30am to 5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Mukund Shah, can be reached on (571) 262-0674. If you are unable to reach Dr. Shah within a 24 hour period, please contact James O. Wilson, Acting-SPE of 1624 at (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

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Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).


Deepak Rao
Primary Examiner
Art Unit 1624

March 7, 2005